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Fibrodysplasia Ossificans Progressiva in Two Half-Sisters: Evidence for Maternal Mosaicism

Hal B. Janoff, Maximilian Muenke, Lyle O. Johnson, Aron Rosenberg, Eileen M. Shore, Enyi Okereke, Michael Zasloff, and Frederick S. Kaplan

Departments of Orthopaedic Surgery (H.B.J., E.M.S., E.O., M.Z. F.S.K.), Genetics (M.M., M.Z.), and Medicine (F.S.K.), University of Pennsylvania School of Medicine, and Division of Human Genetics and Molecular Biology (M.M., A.R.), Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, and The Shriner's Hospital For Crippled Children (L.O.J.), Twin Cities Unit, Minneapolis, Minnesota

Fibrodysplasia ossificans progressiva (FOP) is a rare autosomal dominant disorder of connective tissue characterized by congenital malformation of the great toes and by progressive heterotopic ossification of the soft tissues in specific anatomic and temporal patterns. We observed classic findings of FOP in 2 Native American half-sisters with the same unaffected mother and different unaffected fathers. This is the first report of FOP in sibs from different pregnancies with unaffected parents. The findings in this family indicate the possibility of maternal gonadal mosaicism in FOP and provide important new data for genetic counseling in this disease. © 1996 Wiley-Liss, Inc.

KEY WORDS: gonadal mosaicism, fibrodysplasia ossificans progressiva, heterotopic ossification

INTRODUCTION

Fibrodysplasia ossificans progressiva (FOP) is an extremely rare disorder of connective tissue characterized by congenital malformation of the great toes and by progressive heterotopic ossification in specific anatomic and temporal patterns [Connor and Evans, 1982a; Beighton, 1993; Cohen et al., 1993; Rocke et al., 1994]. Preosseous fibrous nodules arise from soft connective tissues during the first decade of life [Connor and Evans, 1982a; Kaplan et al., 1993b]. The nodules most commonly mature through an endochondral process to form permanent foci of heterotopic bone which bridge and permanently immobilize the adjacent joints [Kaplan et al., 1993b]. In patients who have FOP, mature heterotopic bone is normal biochemically, histologically, metabolically, radiographically, and biomechanically [Kaplan et al., 1994]. Premature death often results from respiratory failure due to severe restrictive chest wall disease [Connor et al., 1981]. To date, there is no effective prevention or treatment.

FOP most often occurs sporadically but a genetic cause has long been suspected on the basis of several reports of identical twins, a paternal age effect, and several descriptions of an affected parent and child [Burton-Fanning and Vaughan, 1901; Gaster, 1905; Vastine et al., 1948; Eaton et al., 1957; Tünte et al., 1967; Rogers and Chase, 1979; Connor and Evans, 1982b; Thornton et al., 1987]. Autosomal dominant transmission with complete penetrance and variable expression has been documented recently in 2 families [Connor et al., 1993; Kaplan et al., 1993a]. The disease is among the rarest genetic disorders with a reported prevalence of 0.61 per million in the United Kingdom [Connor and Evans, 1982b]. Reproductive fitness is extremely low due to the severe disability which develops by early adulthood [Connor and Evans, 1982b; Thornton et al., 1987]. The gene responsible for the disease is unknown. However, genes for bone morphogenetic proteins are possible candidates based on their ability to induce heterotopic endochondral ossification and their ability to regulate pattern formation in the developing skeleton [Kaplan et al., 1990; Tabas et al., 1991].

We describe FOP in 2 half-sisters with different, unrelated fathers and a completely unaffected mother. These findings are compatible with maternal gonadal mosaicism in FOP, and have important implications for genetic counseling in this condition.

CLINICAL REPORTS

The Proposita

The proposita, an 11-year-old native American female, was the product of a full-term gestation and uncomplicated delivery (III-2, Fig. 1). She had short malformed great toes at birth. At one year of age she was unable to extend her neck. At age 13 months, a large firm nodule appeared over the left scapula and ossified

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Address reprint requests to Frederick S. Kaplan, MD, Chief of the Division of Molecular Orthopedics, Department of Orthopedic Surgery, Hospital of the University of Pennsylvania, Silverstein Two, 3400 Spruce Street, Philadelphia, PA 19104.

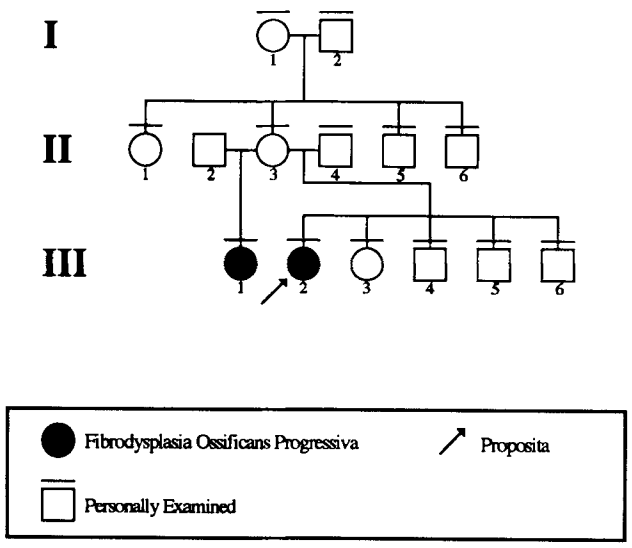

Fig. 1. Family pedigree demonstrates the proband (III-2) who has FOP, her half-sister (III-1) who also has FOP, and their unaffected mother (II-3).

rapidly. She underwent surgery at age 3 years to resect the heterotopic bone overlying the left scapula. Four weeks postoperatively, new lesions appeared and ossified rapidly at the site of the operative procedure. Four intramuscular injections in her right quadriceps led to the formation of 4 foci of ossification at the sites of injection. By age 4 years, she had developed heterotopic ossification about both shoulders, and the diagnosis of FOP was made. At age 5 years, operative resection of heterotopic bone from the left axilla was performed in an attempt to increase the range of motion of her left shoulder, but heterotopic bone recurred within 6 weeks and led rapidly to ankylosis of the shoulder. Heterotopic bone formed at the hips at age 6 years. The right hip became ankylosed by age 9 years. A sublingual injection of novacaine administered during a dental procedure at 9 years of age produced immediate submandibular swelling with subsequent ossification of the omohyoid and myohyoid muscles.

The family (Fig. 1) demonstrated no evidence of FOP in the parents (II-3 and II-4), or in the maternal grandparents (I-1 and I-2). The proposita had one normal sister (III-3) and 3 normal brothers (III-4, III-5, and III-6). She had an older half-sister (III-1) who had less severe manifestations of FOP.

Physical examination showed a large bony bridge spanning the entire cervical region from the occiput to the posterior thoracic cage. The neck was ankylosed in a neutral position. Heterotopic bone bridged the left pelvis to the left posterior thoracic cage, with a resultant right C-shaped thoracolumbar scoliosis. Both shoulders were ankylosed in adduction. The right elbow was ankylosed in extension; the left elbow flexed from 45° to 110°. Range of motion of the wrists and fingers was normal. There was bilateral clinodactyly. The left hip flexed to 90° and extended fully. The right hip was ankylosed in 45° of flexion. Motion of the left knee was normal, but the right knee was ankylosed at 80° of flexion. Nodules of heterotopic bone were palpable in the right quadriceps. No limitation of motion was found in the ankles, wrists, or jaw. The great toes were short with valgus angulation at the metatarsophalangeal joint (Fig. 2A).

Roentgenograms showed delta-shaped proximal phalanges of both great toes (Fig. 2B) and short broad femoral necks (Fig. 2C), findings typical of FOP. There was extensive heterotopic ossification about both hips (Fig. 2C). There was a C-shaped thoracolumbar scoliosis of 55°, with extensive paravertebral heterotopic ossification.

The Half-Sister

The half-sister of the proposita was a 15-year-old Native American female (III-1, Fig. 1). She had short malformed great toes at birth. She was unable to extend her neck as an infant. When she was 5 years old, she received an intramuscular injection in her left triceps muscle. A small focus of heterotopic bone formed at the injection site. At age 12 years, she developed heterotopic ossification of the left posterior chest wall following blunt trauma, and a diagnosis of FOP was made 4 years after the same diagnosis had been made in her younger sister. The disease progressed rapidly to involve the right shoulder and hip. Jaw movement became limited at age 14 years following a dental procedure to fill a cavity.

She had the same mother (II-3) as the proposita (III-2), but a different father (II-2) who was reported to be normal.

Physical examination showed a thin habitus with minimal secondary sexual characteristics. Jaw motion was limited to 4 mm of opening. The cervical spine was ankylosed in neutral. There was symmetrical ossification of the paravertebral muscles and limited motion of both shoulders. There was a nodule of heterotopic bone in the left triceps muscle. The right elbow had 10° of residual movement. There was a flexion contracture of the left elbow. The right forearm was contracted in pronation. Motion of both wrists was normal. There was bilateral clinodactyly. The right hip was ankylosed. The left hip was normal, as were both knees and ankles. There was bilateral microdactyly of the great toes (Fig. 3A).

Roentgenograms showed short first metatarsals with valgus angulation at the metatarsophalangeal joints and monophalangism of the great toes (Fig. 3B). There were congenital fusions of C5 and C6, short femoral necks, and heterotopic ossification bridging the right hip.

The Mother

The mother was a 31-year-old, gravida 6, para 6, Native American female (II-3, Fig. 1). She was healthy and reported no history of fractures, arthritis, skeletal diseases, or spinal problems. The medical history and review of systems were unremarkable.

Physical examination showed a healthy female. She had full range of motion of all joints of the axial and appendicular skeleton. No digital malformations were apparent in either the hands or feet (Fig. 4). There was

neither clinical nor radiographic evidence of heterotopic ossification.

Roentgenograms of the feet were normal.

The Family

Other members of the proposita's family were evaluated in order to determine the presence or absence of FOP. These included I-1, I-2, II-1, II-4, II-5, II-6, III-3, III-4, III-5, III-6. All were healthy and had no history of bone or soft tissue abnormalities.

Physical examination revealed normal joint examinations in I-1, I-2, II-1, II-4, II-5, II-6, III-3, III-4, III-5, III-6 (Fig. 1). No digital malformations were present in the hands or feet. The father (II-2) of the older affected sister (III-1) could not be located for examination.

Molecular Studies

Genotyping was performed on DNA samples from family members (I-1, I-2, II-3, II-4, III-1, III-2, III-3, III-4, III-5, III-6). The father (II-2) of the older FOP patient (III-1) was not available for the study. DNA samples were analyzed by polymerase chain reaction (PCR) by standard protocols using a total of 23 well-characterized, highly polymorphic microsatellite markers (Research Genetics, version 3 and Genethon markers) from 5 different chromosomes [Robin et al., 1994]. Fourteen of the 23 markers (D4S1627, D6S251, D6S271, D8S88, D8S264, LPL, D14S80, GATA5H04, GATA4B04, D20S27, D20S95, D20S102, D20S110, D20S119) were informative with respect to individual alleles of II-3, II-4, III-1, and III-2. Results of this analysis confirmed common maternal alleles but different paternal alleles in the 2 affected half-sisters (III-1 and III-2). II-3 was, in fact, the common parent of both affected children, as well as of the 4 other unaffected sibs (III-3, 4, 5, 6).

DISCUSSION

This is the first report of FOP in 2 sibs from different pregnancies with unaffected parents. The most striking difference between the 2 half-sisters in this family was the rate of postnatal disease progression, which was slower in the older child (III-1) and more rapid in the younger proposita (III-2), although both had similar toe malformations and anatomic patterns of disease progression. We estimate the chance that both sisters developed FOP from independent spontaneous mutations to be less than 3.6×10^{-13} [Connor and Evans, 1982b]. Given the extraordinary unlikelihood of such an occurrence, maternal gonadal mosaicism could better explain the observed familial pattern of disease involvement [Hall, 1988, 1993]. While the mother was phenotypically normal, she may have been a mosaic for the dominant mutation which was fully expressed in 2 of her offspring inheriting the disease allele [Bernards

Fig. 2. Clinical photographs and roentgenograms of the proposita (III-2). **A:** Photograph of feet showing short malformed great toes. **B:** Anteroposterior roentgenogram of feet showing short first metatarsals, valgus angulation of first metatarsophalangeal joints, and delta-shaped proximal phalanges. **C:** Anteroposterior roentgenogram of the pelvis showing extensive heterotopic ossification of both hips, and short broad femoral necks.

Fig. 3. Clinical photograph and roentgenogram of the feet in the older sister of the proposita (III-1). **A:** Photograph of feet showing short malformed great toes. **B:** Anteroposterior roentgenogram of feet showing short first metatarsals, valgus angulation of first metatarsophalangeal joints, and monophalangism of the great toes.

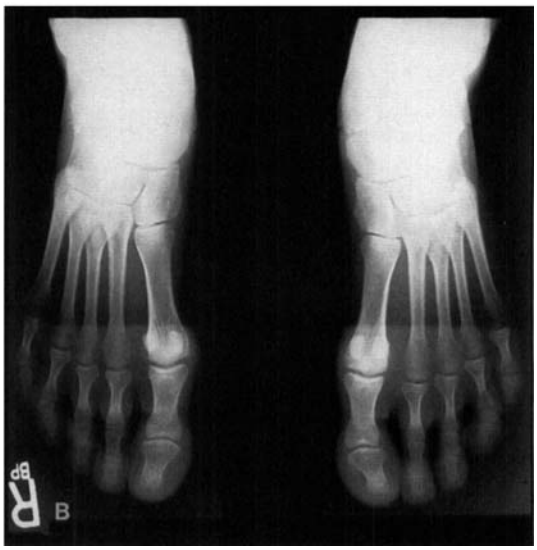

Fig. 4. Clinical photograph (**A**) and roentgenogram (**B**) of the normal-appearing feet in the mother (II-3) of the affected girls.

and Gusella, 1994]. The disease-causing allele may have been restricted solely to the mother's gonadal tissues. Alternatively, her somatic tissues may also have been affected, but the disease allele might not have been present in levels sufficient to cause the disease phenotype [Hall, 1988; Edwards et al., 1992]. The current lack of a genetic marker for FOP precludes definitive investigation of the proposed mosaicism.

The findings in this family require a reassessment of the risk of recurrence of FOP for normal parents who have an affected child. In cases of gonadal mosaicism, the true recurrence risk is related to the degree of mosaicism in the gonadal tissue. Without a genetic marker for FOP, neither the degree of mosaicism nor the frequency of new cases arising from gonadal mosaicism can be adequately determined. Nevertheless, such considerations must be factored into the genetic counseling for families with at least one affected offspring [Bernards and Gusella, 1994]. We feel it is prudent to consider the potential for mosaicism in any sporadic case of FOP when estimating the risk of recurrence [the rate of recurrence due to gonadal mosaicism in several other autosomal dominant genetic disorders may be 5–6%; Byers et al., 1988; Hall, 1988].

Ethnic background in FOP is diverse and there are no reported gender, racial, or geographic predilections [McKusick, 1994]. This family is, to our knowledge, the first Native American family (Chippewa Nation) reported to have FOP, and thus expands the ethnic profile of this rare disorder [McKusick, 1994].

In summary, the 3 notable features of FOP in this unusual kindred are: 1) a family pedigree which supports maternal gonadal mosaicism as the basis for the inheritance of FOP, 2) a variable temporal progression of postnatal heterotopic ossification in the 2 affected half-sisters, and 3) a description of the disease in a Native American family.

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